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EXAMINER	
HARLE, JENNIFER I	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,964	LIU, YA FANG	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,39,40 and 44* is/are pending in the application.

4a) Of the above claim(s) *45-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,39,40 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-35, 37-38, 41-43 are canceled. Claims 45-48 are withdrawn. Claims 36, 39-30 and 44 are pending.

Election/Restrictions

2. Applicants argue that the Examiner's restriction between claims 36, 39-40 and 44 and the later added claims 45-48 is improper, and requests that she withdraw the restriction requirement. The argument is based upon the fact that the examiner is flawed in her reasoning behind the restriction requirement that the first set of compounds acts on the enzyme level, while the second act at the gene level.

The examiner agrees that her reasoning was flawed but not that the restriction itself was improper. The restriction is maintained and the reasoning is clarified as set forth below.

Group I, claims 36, 39-40, and 44, are compounds that block ATP by binding to the ATP binding site. The withdrawn claims are drawn to two separate invention.

Group II, claims 45 (in part) and 47 (in part), is drawn to administration of kinase dead MLK2.

Group III, claim 45 (in part), 46, 47 (in part) and 48, is drawn to the dominant negative SEK1.

The distinction between the three groups is that the inhibitor binds the ATP site. Group II is a kinase that competes for ATP. Group III is a kinase, which is phosphorylated by MLK but does not phosphorylate JNK and does not inhibit MLK activity but does inhibit the pathway. Therefore, they are independent and distinct from each other because they have different biological effects and are structurally distinct.

Thus the restriction is maintained and the later added claims remain withdrawn.

Information Disclosure Statement

3. The examiner thanks Applicant for filing the list of references that was originally filed with Applicant's cover document to the 1449, filed January 9, 2002. Unfortunately, it was never either received or scanned into our system. It will be reviewed with this Official Action, along with the new IDS filed.

Claim Rejections - 35 USC § 112

Enablement Rejection Under 35 U.S.C. § 112

4. Applicant's arguments filed July 11, 2005 have been fully considered but they are not persuasive.

Applicant argues 1) that the Examiner alleges that there is only a hint but no real link in the application that glutamate-mediated neurotoxicity is a common pathway that contributes to neuronal degeneration in a variety of diseases, however, Applicants present several articles to show that excitotoxicity in various neurological diseases and links between Parkinson's and other neurological diseases; 2) that the specification provides a new target for modulating the effects of excitotoxicity; 3) that guidance was provided as to the selection of "suitable compounds" for testing using Applicant's screening assay because the claims recite the use of compounds that block ATP binding to MLK, that they therefore do not need to provide any structure because a certain activity is provided and that the "suitable compounds" defeats the purpose of a screening assay" at least in part; 4) that there is no need to provide guidance on any point mutations of any enzyme to bind to the ATP binding region because the enzymes themselves are specified, that the knowledge of the person skilled in the art clearly includes the knowledge that inhibitors of ATP binding inhibit kinase activity and would be very familiar with ATP binding sites and determination of mutation in such sites to render the ATP binding site in active making any experimentation required strictly routine,

that it is an absolute requirement of kinases that they be able to bind ATP in order to transfer a phosphate to an acceptor site on a target protein and a specific point mutation of MLK2 is provided in Example 3 and a reference of a kinase dead MLK3 molecule was referred to in the prior art in the specification and of apoptosis induced by various compounds and 5) that the examiner's arguments regarding *in vivo* therapy requiring support evidence and working examples is unnecessary because many patents have issued that have *in vitro* activity of the compound and that is essentially what Applicant has provided, i.e. the identification of a relevant target (MLKs) for modulating excitotoxicity and therefore treating Parkinson's disease and a person of skill in the art does not need further disclosure for the specification to enable the treatment of Parkinson's disease.

Enablement is considered by taking into account all of the Wand's Factors in their totality and the instant claims are drawn to a method of treating Parkinson's with compounds that have been identified by a specified neuronal death screening assay. See the previous rejections incorporated by reference.

1) *The breadth of claims/nature of the invention*: As previously set forth the Applicant's claims are drawn to a method of treating Parkinson's with compounds that block ATP binding to MLK by binding to a MLK ATP binding site and that inhibits MLK activity and thereby prevent neuronal cell death occurring in a mammal susceptible to or having Parkinson's disease, preferably by utilizing Applicant's screening assay. The instant claims constitute nothing more than a wish to know compounds that meet a desired criteria. The scope of potential compounds is unlimited.

2) *The state of the prior art/the level of ordinary skill in the art/the level of predictability in the art*: Applicant's argue that the state of the prior art is such that basically all they have to do is describe the mechanism and one of ordinary skill in the art can practice the invention. They cite several pieces of prior art to show that Parkinson's and several other neurological diseases are

linked to excitotoxicity and are linked to each other. They then claim that it is the knowledge of the person of skill in the art that inhibitors of ATP binding inhibit kinase activity and it is an absolute requirement of kinases that the be able to bind ATP in order to transfer a phosphate to an acceptor site on a target protein and that it is very routine to one of ordinary skill in the art with ATP binding sites and the determination of mutation in such sites to render the ATP binding site inactive but provide no evidence. Moreover, it is noted that one would have to know the relevant ATP binding sites while the receptors were disclosed, the ATP binding sites were not. Applicant's first prior art reference regarding excitotoxicity is an abstract from a conference by Sureda (2000) and does not apply to the state of the prior art at the time of the invention, i.e. 1998, however, even in Applicant's own quote, it only **postulates** a role for exictotoxicity for Parkinson's, Alzheimer's, Huntington's, and does not provide an affirmative link and does not link glutamate receptors to Parkinson's and the only mention of the potential of the drugs is that they attenuate "some of the pathological symptoms in experimental models of acute and chronic neurodegenerative diseases." Applicant states that Fornai, et al. discloses that experimental parkinsonism is prevented by NMDA antagonists, however, Fornai does not make such a final conclusion. Instead, he conducts a series of studies and discusses others, some where NMDA antagonists work on experimental parkinsonism and some where it does not. Fornai discloses that the role of exitotoxicity in the mechanism of action of MPTP is less clear, and that despite extensive studies, the intimate cause of Parkinson's disease is unknown, and so are the pathological agents which induce the selective degeneration of dopaminergic neurons occurring in this idiopathic disorder and that no single mechanism can be considered solely responsible for neuronal death in Parkinson's disease but that is has been suggested that excitotoxicity might represent a final common pathway which operates independently of specific causes of neuronal damage, he concludes that although the **interaction of**

NMDA antagonists with MPTP in different experimental conditions are **not completely clear**, the overall evidence makes it **conceivable** that excitotoxicity participates in the cascade of MPTP-induced toxic events ... The **hypothesis** of a relationship between exictotoxicity and mitochondrial abnormalities, supported by the MPTP model, has aroused wide interest among neuroscientists not only as a mechanism for nigrostiratal damage but also as a more general feature of the pathogenesis of neurodegenerative diseases (note that the interactions are not clear and it is only a hypothesis). Thus, we are still left with only a hypothesis and no clear link. Olney specifically states that despite several decades of research aimed at elucidating the mechanisms underlying neuronal degeneration in Parkinson's and Huntington's diseases, these mysteries remain unfathomed and that while the brain contain high concentration of putative transmitters, glutamate and aspartate, which have neurotoxic (excitotoxic) potential and are thought to cause neuronal degeneration, in certain acute neurological disorders, no mechanism has been identified by which these diffusely distributed agents might cause the regionally selective patterns of neuronal degeneration characterizing Parkinson's and Huntington's diseases. Olney then goes on to **propose** that an excitotoxic process mediated by L-DOPA or an acidic derivative such as 6-OH-DOPA **might be** responsible for degeneration of nigral neurons in Parkinson's disease or striatal neurons in Hutington's disease. Olney's conclusions are filled with the qualifications and speculations none of which are more than hypotheses of "these findings are consistent with the interpretation that both L-DOPA and 6-OH-DOPA have intrinsic excitotoxic properties that could contribute to the pathophysiology of neurodegenerative diseases ... **If L-DOPA or an excitotoxic derivative were generated in excessive amount** within the cell bodies of DOPA containing nigral neurons and leaked from these neurons into the extracellular compartement immediately surrounding them, this **would be an excellent formula for selective excitotoxic degeneration** of substantia nigr doaminergic neurons

(Speculation). Similarly, an aberrant mechanism conducive to buildup of L-DOPA or an excitodoxic derivative in nigrostriatal dopaminergic axon terminal and leakage from these terminal **would readily explain** the pattern of neuronal degerneration in Huntington's disease ... **If the mechanism** for converting DOPA to dopamine in these terminal were defective, **it might cause** both an accumulation of DOPA or its derivatives ... **If the above hypothesis is correct** with respect to **either Parkinson's or Huntington's** disease, our finding that an anti-excitotoxic drug protects against either L-DOPA or 6-OHDOPA neurotoxicity **suggests** that it **may be possible** to devise a chemoprophylactic approach for preventing neuronal degeneration **in one or both** of these diseases. Thus, Olney does not establish a link between the two diseases or even that excitotoxicity plays a role in either, merely an hypothesis that something may be occurring that provides an explanation. Applicant states that Thomas discloses Parkinson's and Alzhimer's diseases are only some of the neurological disorders in which excitatory amino acids play a major role. However, Thomas states that the study of physiological and pathological aspects of excitatory aminoacid (EAA) neurotransmission is currently one of the most exciting areas of basic and applied neuroscience having profound relevance to older people especially in the management of stroke, seizures, pain, Parkinson's disease and possibly Alzheimer's disease (pg. 1279), however, the only link with Parkinson's is a mouse study from 1991 using one NMDA antagonist MK-801 (which was withdrawn from human experimentation) and he specifically states that "glutamate mediated toxicity has been proposed as a mechanism of neuronal damage in several disease states: confirmation or rebuttal will await further understanding of the role of receptor subtypes and genetic linkage of receptor to genes to disease. Pg. 1288. The only other drug discussed for treating Parkinson's memantine has a plethora of activities among which is blocking NMDA rector-mediated responses in a use-dependent fashion, however, it inhibits binding of dizoclipine to brain

membrain, blocks nicotinic acetylcholine as well as the 5-HT3 subtype or the 5-hydroxytryptamine receptor family. Thus, as Thomas stated, we will have to await further confirmation and understanding, especially in light of animal studies being unpredictive as previously set forth as a model for Parkinson's. Applicant suggests that Doble discloses that animals models suggest that drugs that block glutamatergic neurotransmission might be beneficial in Parkinsons disease, Huntington's disease and ALS, however, Applicant fails to finish Doble's sentence which concludes "but the relevance of these animal models to the human pathology is not clear." Moreover, Doble only suggests that the drugs might be beneficial for the diseases and states prior to that sentence "For chronic neurodegenerative diseases, the role of excitatory amino acids is much less clear". Summary. Moreover, Doble states "there is no *a priori* reason to suspect that excitotoxic mechanisms may be involved in the primary aetiopathology of this [Parkinson's] disorder, although it is always possible that they **may be** involved in determining the extent or rate of progression of the neurodegeneration and that the MPTP test for Parkinson's as the model demonstrating that it follows an excitotoxic process **still remains somewhat controversial**. Pg. 331. Once again, there is supposition but lack of proof and even the neurological community believes that even in the animal model it is somewhat controversial. Pp. 331-332. Applicant contends that Utti and Calne find that Parkinson's , Alzheimer's and ALS result from similar pathological processes. Actually, the direct quote is "Because of the compelling evidence indicating common clinical and pathological finding in idiopathic parkinsonism, Alzheimer's disease, and amyotrophic lateral sclerosis, we believe that these conditions result from pathological processes with more similarity than diversity. A primary glutamarergic cell neocorical abnormality provides an attractive unifying explanation which may explain the overlapping abnormalities found in idiopathic parkinsonism, Alzheimer's disease, and amyotrophic lateral sclerosis." Abstract. Utti

concludes that much more investigation is required to explore the possibility of an excitotoxic pathologenesis for idiopatic parkinsonism even taking into account the protection of substantia nigr neurons from MPTP-induced neurodegeneration and subsequent parkinsonism in primates and the prevention of methamphetamine against dopaminergic nigrostraital neurons. Pg. 14. Utti and Calne **base their hypothesis** upon epidemiology, clinical observations, chemical and metabolic data, as well as PET and histological data and start by stating **that various hypothesis exist to explain the pathogenesis of idiopathic parkinsonism** and that in an attempt to unify idiopathic parkinsonism, AD, and ALS, it has been suggested that these are all phylogenetic diseases of human neocortex involving neurons which make monosynaptic, glutmatergic connection with neurons in the caudate and patmen in idiopathic parkinsonism, with entorhinal cells of the hippocampus in AD, and with motor neurons in ALS. However, Utti and Calne **suggest** that the pathogenesis of idiopathic parkinsonism is likely to be multifactorial, deriving from environmental factor(s) acting upon a genetically predisposed individual and that **because of evidence indicating** common clinical and pathological findings in idiopathic parkinsonism, Alzheimer's disease, and amyotrophic lateral sclerosis appears overwhelming, we **conclude** that conditions result from pathological **processes with more similarity than diversity**, i.e. a primary gluatmatergic cell neocortical abnormality **provides an attractive unifying explanation** (while the **primary cause** for such an abnormality **remains open to speculation** and future research should evaluate pathogenic mechanisms which could result in overlapping abnormalities as found in idiopathic parkinsonism, idiopathic dementia, and amyotrophic lateral sclerosis). Pg. 17. Once again it is speculation and hypothesis and does not correlate with the other references, i.e. exitotoxicity is not deemed relevant here.

Applicant argues that one of skill in the art does not need anything more that what is disclosed to make and use the invention to treat Parkinson's because many patents have issued for

compound to humans with the basis being the biological (*in vitro*) activity of the compounds. However, Applicant's have not provided any Parkinson's *in vitro* testing activity for any compound. Additionally, as previously set forth *in vitro* and even animal studies do not seem to be correlated. See Doble, Abstract. Betarbet, et al. (2002) and Shimohama, et al. (2003). Moreover, while animal models exist, no animal aside from humans suffers from Parkinson's and thus, it must be induced chemically -- the most prevalent being the MPTP, which has to be used on primates. Planning Appeal by University of Cambridge Proposed Primate Research Facility Planning inspectorate Reference APP/WO530/A/02/1090108 Proof of Evidence Parkinson's Disease, November 26, 2002, pp. 1-4. However, the MPTP model has many deficiencies, which make it far from ideal – for example it does not produce the same effects in all the primates injected (some had cognitive deficits and no motor deficits, others had full parkinsonism that was produced after short term exposure high dose exposure, and some had full parkinsonism after long-term low dose exposure), unlike human Parkinson's, which is progressive, the neurotoxic damage is reversible and therefore it is difficult to ascertain the roles played by individual dopamine receptors in the pathology as well as the therapy of Parkinson's and these animal models can only reproduce data already gleaned from humans thus making their predictive value negligible becausle while it is relatively easy to kill the substantia nigra with these substances and make animals shake, the reasons the cells in the substantia nigra die in the animal is not the same as in Parkinson's. Id. pp. 2-4. Moreover, as Applicant's own reference showed MK-801 was pulled from human clinical trials (see above) and the only MLK inhibitor, CEP-1347, known to make human clinical trials was pulled because the data are unlikely to provide evidence of significant effect. See Cephalon, Inc. Press Release, May 11, 2005. Accordingly, the availability of relevant model systems with which to practice the testing is not established. Thus, the level of predictability in the art is highly unpredictable as set

forth above and as Applicant's have not provided even one compound and the only known compound which would meet Applicant's limitations and actually made it to human clinical trials was withdrawn.

3) *The amount of direction provided by the inventor/the existence of working examples*: Applicant's argue that they have provided guidance because excitotoxicity is linked to neurodegenerative diseases, i.e. Parkinson's, as argued in the references and the specification provides a new target for modulating the effects of excitotoxicity, i.e. the use of compound that block ATP binding to MLK, which may but do not need to be identified using Applicant's screening assay. The references have been argued above and are not deemed persuasive for those reasons. As previously argued, blocking ATP binding to MLK is new matter. Additionally, Applicant's argue that in Example 3 they show a specific point mutation of MLK2 and reference a kinase dead MLK3 molecule that was known in the prior art. First Example 3 does not reference a kinase dead MLK3 molecule. Second, the specific point mutation of MLK2 (kinase dead MLK2) is not a teaching of an inhibitor binds the ATP site. Rather it is a kinase that competes for ATP and thus is not providing any guidance towards the inhibitor. Applicant's argument that additionally mutation may be made to MLK to inactivate the ATP binding site would be routine to one of ordinary skill and that any experimentation would be strictly routine does not take into account the fact that Applicant provides no guidance on the binding pocket itself or any other binding pockets for ATP for any other molecules and that this is more than just routine experimentation, as one would still have to determine the molecule, then the binding pocket, then the specific mutation, then does it inactivate the ATP binding pocket, then does it provide any anti-Parkinson's effect at all. Moreover, this is to a non-elected group. Applicant's next argue that Figure 11 shows the effects of a dominant negative SEK1 molecule in inhibiting apoptosis induced by wild type MLK. Once

again this is a kinase, which is phosphorylated by MLK but does not phosphorylate JNK and does not inhibit MLK activity but does inhibit the pathway. It does not teach an inhibitor and thus does not provide any guidance towards the inhibitor. Applicant's provide no working examples in the disclosure which treat Parkinson's that block ATP binding to MLK by binding to a MLK binding site and that inhibits MLK activity.

No compounds have been presented in the disclosure, which are identifiable by structure and function or by the screening assay at all, let alone compounds, which may be used to treat Parkinson's. Clearly lacking any compounds, there is no evidence presented that there are compounds that can treat Parkinson's. The instant claims constitute noting more than a wish to know compounds that meet a desired criteria. It would require a substantial inventive contribution for the person of ordinary skill in the art to find suitable compounds. They would have to identify suitable agents that meet the desired criteria to screen, screen them, and finally determine if the screened compounds have the desired activity. While the second and third steps are tedious and difficult with the assays presented, presumably they could be performed. However, the first step involves substantial inventive contribution. The only "guidance" on narrowing the universe of all possible compounds to any subset of compounds that may be found is to meet the desired condition. In chemistry there is a necessary triumvirate of structure-function-reactivity. The disclosure has not established or disclosed any structure that can meet the desired function or reactivity as an inhibitor. There is no evidence that the person of ordinary skill in the art already has a reasonable expectation of finding such compounds. It is noted that there is not a single example in the instant specification, working or prophetic of compounds that treat Parkinson's. Since there are **no** working examples, then one must consider the guidance provided by the instant specification and the prior art of record. As previously set forth the instant specification provides absolutely no guidance as to the structure

of any suitable compounds to be used in the treatment method. Further, there are no analogous compounds which have been identified in the prior art for which this information is known and could be extrapolated to the instant method by analogy. In conclusion, the instant claim encompasses a vast, almost limitless, number of compounds and yet the instant specification provides no working examples and no guidance Applicant's arguments about excitability, does not lead to teachings of compounds, but is more functional limitations and as discussed above is not predictive of a treatment, and its link with neurological diseases, specifically Parkinson's was not persuasive. Additionally, even assuming that a screening assay would provide inhibitors of MLK enzyme that blocks ATP binding to MLK by binding to a MLK ATP binding site, the disclosure does not enable the use of such inhibitors to treat Parkinson's so as to prevent neuronal cell death. The disclosure merely speculates that inhibitors, if they were available, could be used to treat Parkinson's. If we do not use Applicant's screening assay, then what guidance has been provided at all? No structure has been provided only functional language and as previously set forth with no guidance on how to select any compound this is merely a wish. Since there are no working examples of treatment with even a model system with inhibitors of MLK enzymes, it cannot be seen how the disclosure could enable such treatment *in vivo*. Applicant's arguments that a person of skill in the art need only conduct routine experimentation in order to determine appropriate amounts of a compound that block ATP binding to MLK that are both safe and efficacious and that they have provided the basis for the treatment being the biological (*in vitro*) activity of the compounds, the identification of the relevant target does not even answer the Examiner's arguments of even *in vitro* data or models, let alone the unpredictability of treating Parkinson's with these type of compounds.

There must be specific guidance, not general as to the nature and manner of compounds that will be used in the desired therapy. Contrary to the assertions in response, it would take a

considerable amount of experimentation to find a useful product. One would have to establish the relevance of a particular animal model to the proposed pathway. One would have to screen for a compound that blocks the proposed pathway. One would have to screen from among those inhibitor compounds those that actually act on the animal model in the desired manner. Finally, one would have to have a reasonable expectation that the studies with the animal model would extrapolate to the human disease. None of these elements had been done at the time the invention was made. The combination of these does involve undue experimentation because there clearly is an undue burden at several of these steps. Thus, claims 36, 39-40 and 44 remain rejected under 35 U.S.C. 112, first paragraph, as not being enabled.

New Matter Rejection Under 35 U.S.C. § 112

5. Applicants argue that the recitation in the claims of compounds that block ATP binding to MLK by binding to a MLK ATP binding site is not new matter because Applicant provided a description of this in Example 3, which discloses the mutation of a binding site to prepare a kinase dead MLK2 and references a paper by Tibbles, et al. that provides kinase-dead mutants of MLK-3. First, the Examiner notes that in Example 3 the disclosure of the mutation of a binding site to prepare kinase dead MLK2 does not teach that this point mutation, as previously argued and that the link between the compound and it use is supported by that known by one of ordinary skill in the art and that excitotoxicity is a common pathway for the action of different neurotoxins, and therefore, that blocking excitotoxicity would be expected to be effective in treating neurodegenerative diseases, as set forth in the enablement rejection. This is not found persuasive for the same reasons set forth in the enablement rejection. As set forth above, one of skill in the art would not have found that excitotoxicity was enough for there to be an effective mechanism of treatment for a therapeutic of Parkinson's. The links between Huntington's and Alzheimer's that Applicant

attempts to establish via the prior art are full of qualifiers, hypotheses, hints and suggestions. Thus, for the reasons previously set forth and those set forth herein Applicant's arugments are not persuasive and claims 36, 39-40 and 44 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Written Description Rejection Under 35 U.S.C. § 112

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, no that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been

placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention*.

In the instant case, the claims are drawn to a method for treating Parkinson's disease in a mammal (noting that only humans are the subjects of naturally occurring Parkinson's disease) using an unspecified compound described by the compound's desired function of blocking ATP binding to MLK by binding to a MLK ATP binding site and that inhibits MLK activity and thereby prevents neuronal cell death occurring in a mammal susceptible to or having Parkinson's disease.

(1) Level of skill and knowledge in the art:

As set forth under the enablement rejection the level of skill in the art is high. The knowledge in the art is such that no compounds were known that exhibited that activity. Applicant's argue that excitotoxicity was known to be a factor in neurological diseases in general and Parkinson's in particular and cite several references. These references are discussed above and are full of hypotheses, suggestions and speculation but at most speculated that excitotoxicity was an area of research for potential therapeutics. Applicant's also cited art that they stated suggested

links between various neurological diseases. These references too are iscussed above and are full of hypotheses, suggestions and speculation. None of the references cited were deemed persuasive for the reasons set forth above. Even assuming arguendo that excitotoxity played any role in Parkinson's, the references did not establish that a therapeutic would have any effect or that one would expect receptors of MLK to have a role. In fact, the references clearly stated that further research into the receptors and mechanisms of action was necessary to determine their roles in excitotoxicity. See above.

(2) Partial structure:

No partial structure was given that can act as an inhibitor. Applicant's argue that kinase dead MLK-2 and dominant negative SEK-1 are set forth, however, they act by different mechanisms of action, as set forth above.

(3) Physical and/or chemical properties:

The physical and/or chemical properties set forth could be blocking ATP binding to MLK by binding to a MLK ATP binding site but this could also be interpreted as a functional characteristic, as it does not clearly set forth property that has any real metes and bounds, it is fluid because the compounds can bind in a number of ways at a number of positions within the MLK and is described functionally rather than in set terms.

(4) Functional characteristics:

See above. Inhibition of MLK activity and prevention of neuronal cell death occurring in a mammal susceptible to or having Parkinson's disease.

(5) Method of making the claimed invention:

An assay is provided for determining inhibitors but there is no method for making any inhibitors set forth and to argue that one can make material embodiments of the claimed invention

and then test for those that work in the manner disclosed is unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them then the instant application does not support the making of the claimed invention. In the instant case, as previously set for it is highly improbably that any compound known or unknown will more likely than not perform in the manner disclosed and the instant specification does not provide the guidance need to produce these compounds with any reasonable expectation that the resulting compounds will function as an therapeutic for Parkinson's in the manner claimed.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claims 36, 39, 40 and 44 are all broad generics, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of chemical, peptide, protein, etc. compounds. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds because no compounds are disclosed in the specification. Even assuming arguendo, that dead kinase MLK2 and dominant negative SEK1 (which operate over different pathways and are not demonstrated to treat Parkinson's) the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the

specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

6. Applicant's argument, that Miller is not enabled for the same reason that Applicant's application is not enabled, filed July 11, 2005, with respect to Miller, et al. have been fully considered and are persuasive. Noting that it would also be withdrawn because it now would lack written description for the same reasons. The rejection of claims 36, 39, 40 and 44 has been withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer I. Harle
Examiner
Art Unit 1654

October 18, 2005